REMARKS

Claims 1-9 are pending in the instant application. Claims 1-9 have been rejected. Claim 1 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §112

Claims 1-9 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1-9 are drawn to a method of stably expressing a selected DNA sequence in the central nervous system of a mammal. The Examiner suggests that the specification provides no use for mere stable expression other than for gene therapy. The Applicants respectfully traverse this rejection.

The claimed invention is a tool for introducing nucleic acid sequences into a particular group of cells such that they are expressed for a long period of time. The specification provides evidence in an animal model of MPS VII, that a neurotropic virus can be used to deliver a transgene to the CNS of said animal such

that said transgene is expressed for at least four months. While the specification provides gene therapy as on use for the method of the invention, it does not restrict the utility of the method to gene therapy. See bridging paragraph of pages 9 and 10 of the specification which provides examples of molecules that may be stably expressed in the central nervous system without restricting their use to gene therapy. At the time of filing, the state of the art was such that the skilled artisan could envision other uses for such molecules including establishing an animal model. See, for example, King et al. ((1994) J. Immunol. 153:4059-4069) who teach a tissue-specific transient transgene model for investigating cytokine functions *in vivo* by intratracheal administration of a recombinant human type 5 adenovirus with rat IL-6 cDNA incorporated into the E3 region of the viral genome. This approach led to a highly compartmentalized overexpression of the IL-6 transgene and production of bioactive protein within the lung. Similarly, one may use the method of the invention to generate an animal stably expressing, for example, an antisense or overexpression construct in the central nervous system to produce an animal model of a disease associated with the central nervous system. This animal model may be used to better understand the factors associated with the disease and its

progression such that more effective diagnostic tools may be found. Such an animal would be further useful for identifying agents which may be used to prevent or treat the disease associated with the central nervous system.

The Examiner suggests that the state of the art at the time of filing was not developed sufficiently that mere showing of delivery of a gene to a particular tissue would be viewed as enabling gene therapy. The Examiner provides several general commentary articles that summarize the art of gene therapy at the time of filing and suggests that the art indicates that vector, vector delivery and extent of expression were critical limitations to gene therapy. As a whole, the references of Verma ((1997) *Nature* 389:239-242), Marshall ((1995) *Science* 269:1050-1055), Anderson ((September 1995) *Scientific American* 124-128), and Blau ((Nov. 2, 1995) *New Engl. J. Med.* 1204-1207) are directed to the more commonly used vector systems of the time: adenoviruses, adeno-associated viruses, retroviruses and lentiviruses, and provide a limited understanding of the art for using neurotropic viruses to deliver genes to the CNS. The Examiner further provides references specifically teaching the use of HSV-1 vectors and suggests that the use of these vectors in gene therapy protocols was unpredictable. The Examiner cites

Fink et al. ((1996) *Clinical Neuroscience* 3:284-291) who indicate that with first generation HSV vectors, such as those specifically taught in the specification, but that expression of the DNA sequence of interest was not for a sufficient length of time for effective treatment of neurodegenerative disease. It is further pointed out in Fink et al. that HSV vectors applied to gene therapy protocols exhibited a residual toxicity resulting from non-replicating vectors and silencing DNA sequence expression from persisting latent HSV genomes in neurons (page 284, abstract). The Examiner further cites Blömer et al. ((1995) *Human Mol. Genet.* 5:1397-1404) and Eck and Wilson ((1996) *In*: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 9th Edition, McGraw Hill, pp. 77-101), suggesting that these references indicate the potential use of HSV as gene therapy vectors, but that the spread and cytotoxicity of the virus restrict its use.

While the teachings of Fink et al. may indicate that length of time of transgene expression was an unpredictable parameter of gene therapy, the use of HSV for gene transfer was predictable. With regards to toxicity and viral spread, Fink et al. demonstrate that in vivo, replication-defective recombinant HSV show little evidence of cytotoxicity by standard histological

measures of cell destruction or inflammatory response and that these vectors, despite their inability to replicate in brain, are able to establish latency (page 239, column 2, §3, lines 1-8). Thus, in light of the teachings of Fink et al., the unpredictability of using HSV for gene therapy is primarily due to the parameter of length of time of transgene expression. The present application specifically addresses this unpredictable parameter by teaching and demonstrating that a selected DNA sequence is stably expressed for at least four months. See page 19, lines 29-32.

The Examiner further cites Wolfe et al. ((1992) *Nature Genetics* 1:379-384) who show that when an HSV-1 construct containing a cDNA encoding β-glucuronidase was administered to MPS VII mice via corneal abrasion, glucuronidase positive staining cells were identified but that quantitative measurements of β-glucuronidase activity would not be made because there was too little enzyme for analysis.

While Wolfe et al. indicate that too little enzyme was present for measurements of β-glucuronidase activity, they also indicate that since the intensity of staining has been shown to correlate with quantitative measurements of enzymatic activity, that the vector-corrected cells may have been expressing near

normal amounts of GUSB. Furthermore, Verma (*supra*) states that gene transfer to just a few hundred cells of the brain could considerably benefit patients with neurological diseases (page 239, paragraph bridging columns 2 and 3). Thus, while Wolfe et al. state that "two few cells have been corrected at this state to alter the disease phenotype" in the experiments provided therein, it would be reasonable to expect from the teachings of Fink et al. in combination with the teachings of Verma, that if one could overcome the unpredictability of length of transgene expression from an HSV vector and provide expression of a transgene in just a few cells of the brain, one could considerably benefit patients with neurological diseases. Thus, as the present invention has taught one how to overcome the unpredictable parameter of length of transgene expression, the skilled artisan could apply the method of the invention to gene therapy with an expectation of successfully expressing a transgene in the CNS for at least four months.

Accordingly, the Applicants believe that the application provides a sufficient description to enable one reasonably skilled in the art to make or use the invention from what is provided in the disclosure coupled with information known in the

art without undue experimentation. It is therefore respectfully requested that this rejection be withdrawn.

II. Rejection of Claims Under 35 U.S.C. §102

Claims 1 has been rejected under 35 U.S.C. §102 (b) as being clearly anticipated by Palella et al. (1989) *Gene* 80:137-144. Palella et al. teach the infection of mouse brains by intracranial injection of an HSV-1 vector comprising a DNA sequence encoding human *hprt* operably linked to an HSV-1 thymidine kinase promoter. The examiner suggests that *hprt* expression observed in brain extracts was not transient as it was detected up to 5 days after inoculation. Applicants respectfully traverse this rejection.

In an effort to advance the prosecution, Applicants have amended claim 1 to recite that a selected nucleic acid sequence is stably expressed for at least four months. While, Palella et al. show *hprt* expression in brain extracts of mice 5 days after inoculation with an HSV-1 vector containing the human *hprt* gene expressed from an HSV-1 thymidine kinase promoter, this reference does not show stable expression of *hprt* in brain extracts for more than 5 days (see Figure 5, lanes 7-9 and page 142, col 2, 4

1, lines 4-7). The instant specification indicates that stable expression is reached by expression of the transgene over a long period of time (i.e., greater then 4 months). See page 19, lines 29-32. Therefore, Palella et al. do not anticipate claim 1 as this reference does not show expression of the HSV-delivered transgene in the central nervous system for at least four months. It is therefore respectfully requested that this rejection be withdrawn.

III. Rejection of Claims Under 35 U.S.C. §103

Claims 1-9 have been rejected under 35 U.S.C. §103 (a) as being unpatentable over Palella et al. (1989) Gene 81:137-144 and Dobson et al. (1989) J. Virol. 63:3844-3851 in view of Nishimura et al. (1986) Proc. Natl. Acad. Sci. USA 83:7292-7296.

Palella et al. teach the infection of mouse brains by intracranial injection of an HSV-1 vector comprising a DNA sequence encoding human hprt operably linked to an HSV-1 thymidine kinase promoter. Analysis of brain extracts demonstrated the presence of human hprt DNA sequences indicating expression of the selected DNA sequence operably linked to a selected promoter. Dobson et al. teach the delivery of rabbit a-

globin gene to the peripheral nervous system of mice where expression of the gene is regulated by the HSV-1 latency promoter. As acknowledged by the Examiner, Palella et al. and Dobson et al. do not teach delivery to the central nervous system nor the delivery of β-glucuronidase or tyrosine hydroxylase linked to a promoter. Nishimura et al. teach the DNA sequence encoding for β-glucuronidase.

The Examiner suggests that Palella et al. offer the motivation in stating that the system that they describe demonstrates transfer and expression of human gene sequences in brain after an *in vivo* infection with recombinant HSV-1, but that there are problems with the system. The Examiner also suggests that further motivation is found in Dobson's teachings that HSV can produce latent infections in both the PNS and CNS, and that the latency activated promoter, the LAT promoter, is active in such infections. Thus, given the teachings of Palella et al. that HSV-1 can successfully transfer a human gene and express the gene in infected mouse brains, of Dobson et al. that an HSV-1 vector delivers a gene of interest to the PNS and regulates expression of the gene from the LAT promoter, and that HSV inherently infects both the PNS and CNS and of Nishimura teaching a DNA sequence encoding human β-glucuronidase, it would have been

obvious to the ordinary artisan at the time of filing to deliver a gene of interest, such as human β-glucuronidase, to the CNS by administering the vector of Dobson et al.

Applicants respectfully traverse this rejection.

MPEP § 2143 states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations.

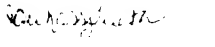
The primary reference of Palella et al. fails to make the instant invention obvious for the same reason it does not anticipate the instant invention; it does not teach stable expression of a transgene in the central nervous system for at least four months. As Dobson et al. do not show central nervous system-localized expression of a transgene delivered by an HSV-1 vector or expression of the transgene over a long period of time (i.e., greater then 4 months), this reference fails to remedy the deficiencies of the primary reference. Likewise, Nishimura et al. do not teach stable expression of a transgene in the central

nervous system for at least four months. It is therefore respectfully requested that this rejection be withdrawn.

IV. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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Date: **March 10, 2003**

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